

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dosuk D. Lee et al.	Confirmation No.:	5068
Serial No.:	09/153,133	Art Unit:	1627
Filed:	September 15, 1998	Examiner:	Layla Soroush
Customer No.:	21559		
Title:	CALCIUM PHOSPHATE DELIVERY VEHICLE AND ADJUVANT		

DECLARATION OF DR. MICHAEL STRUNK UNDER 37 C.F.R. § 1.132

I, MICHAEL STRUNK declare:

1. I am an employee of ETEX Corporation, the owner of United States Patent Application Serial No. 09/153,133.

2. I have read and understood the non-final Office Action dated May 17, 2010, and the references cited by the Office, Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld"), Antonucci et al. (U.S. Patent No. 5,508,342; hereinafter "Antonucci"), and Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter "Gerhart"), and I fully understand their technical content. This Declaration is presented to overcome the rejection of claims 45, 46, 58, 59, 73, and 75-77 under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Antonucci and Gerhart.¹

3. I received a Ph.D. in chemistry at the University of New Mexico. I am currently employed as a chemist at Etex Corporation. My education and professional experience are described in further detail in my curriculum vitae, a copy of which is attached as Exhibit A.

¹ Claim 78 was inadvertently omitted by the Office in its summary and examination of the pending claims. The statements herein apply equally to claim 78.

4. The present claims are directed to a composition that includes amorphous calcium phosphate (ACP) or poorly crystalline apatitic calcium phosphate (PCA) and an antigen or vaccine, in which the composition is formulated as an injectable paste that hardens in an endothermic reaction at body temperature to form a PCA calcium phosphate. In contrast, the compositions described in Antonucci and Gerhart harden in an exothermic reaction. It would not be possible to achieve the composition of present claims 45, 46, 58, 59, 73, and 75-78 by using the composition of Relyveld, Antonucci, or Gerhart, whether considered alone or in combination.

5. Relyveld describes an aqueous gel formulation that contains particles of calcium phosphate. One of skill in the art would recognize that the gel of Relyveld remains particulate and does not harden into a PCA calcium phosphate solid. For example, the abstract states that the gel has "a settling rate of 1 to 20 mm in 10 minutes at 20°C when containing 0.07 atoms of Ca per liter." In contrast, the delivery composition recited in pending claims 45, 46, 58, 59, 73, and 75-78 is a paste formulation that hardens in an endothermic reaction at body temperature to form a solid PCA calcium phosphate. In addition, Relyveld states that the calcium phosphate in its gel has a structure similar to tricalcium phosphate ($(\text{PO}_4)_2\text{CA}_3$). In contrast, PCA calcium phosphate has a structure corresponding to $\text{CA}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$ (see, e.g., Table 1 on p. 224, and p. 230 of Dorozhkin, *Materials* 2:221:291, 2009; and p. 11 of Combes et al., *Journal of Biomedical Materials Research, Part A*, 7:318-328, 2006)), which is distinct from the calcium phosphate of Relyveld, and would be so recognized by one of skill in the art.

6. The Gerhart composition does not harden in an endothermic reaction at body temperature. The Gerhart composition was tested for its heat of formation relative to an ACP composition prepared as disclosed in the present specification.² The Gerhart composition was prepared by hydrating one kit of polymethylmethacrylate (40 g, Lot #043P/0031) powder (polymethylmethacrylate, benzoyl peroxide) with liquid (methyl methacrylate, butylmethacrylate, N,N dimethyl-p-toluidine) and mixing to a uniform consistency in a blue PETG jar. 6.7g of the hydrated paste was combined with 7.5 g β -tricalcium phosphate (Fluka,

² The ACP composition was tested in the absence of an antigen or vaccine. The presence of the antigen or vaccine would not alter the endothermic hardening properties of the composition.

Lot #407381/1 31700) and CaCO_3 (EM Science, Lot #43073419) in an 8 oz. (236 mL) mixing cup.

Twenty-five grams of ACP (Lot #212-045) was prepared by mixing with deionized water to form a uniform paste.

Nested styrofoam insulated calorimeters were prepared. Equal masses of each experimental material were added to individual calorimeters, immediately after mixing to paste consistency. A calorimeter filled only with water was used as a control. Then 150 mL of H_2O at 35°C was added to each. The three calorimeters were then sealed with styrofoam insulated lids to create a closed system. Two Type K thermocouples were inserted through the lid of each calorimeter; these were connected to an Agilent 34970A Data Acquisition MUX (EN0717). The temperature changes in each calorimeter were monitored using Agilent BenchLink Data Logger Software (v. 1.4.000512). The calorimeter containing only water was monitored on channels 201 and 202; the one containing the Gerhard composition was monitored on channels 203 and 204; the one containing ACP was monitored on channels 205 and 206.

7. As shown in Exhibit B, the heat lost from the system by the reference cell equals 6270 Joules/gram (J/g), the heat added to the system by the experimental cell containing the Gerhard composition equals 9929J/g (corrected for system heat loss), while the heat lost from the system by the Experimental cell (ACP - ETEX) equals 2106J/g (corrected for system heat loss). Thus, the calorimetry data show that the Gerhart composition hardens in an exothermic reaction, whereas the ACP composition hardens in an endothermic reaction.

8. Antonucci describes a curing reaction using unsaturated monomers, such as acrylates and methacrylates, that is similar to the curing reaction described by Gerhart. Curing reactions, such as those described by Antonucci and Gerhart, occur when the unsaturated monomers polymerize, which produces an exothermic reaction that releases heat rather than an endothermic reaction that removes heat from the system, as occurs during the hardening reaction that produces the delivery composition of present claims 45, 46, 58, 59, 73, and 75-78. The curing of acrylates and methacrylates in an exothermic reaction is well documented (see, e.g., BASF Corporation, "Acrylic Acid: A Summary of Safety and Handling," 3rd Edition; Atkinson and Grant, *J. Dent. Res.* 44:1040, 1965; Rohm and Hass Technical Bulletin; Knets et

al., *J. Achieve. Mater. Manuf. Eng.* 20:135-138, 2006; and Saltzman et al., *J. Orthop. Sports Phys. Ther.* 30:56-67, 2000).

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: June 17, 2011

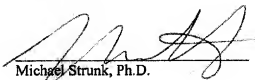

Michael Strunk, Ph.D.

Exhibit A

Curriculum Vitae

Michael R. Strunk, Ph.D.

ETEX Corporation
38 Sidney Street
University Park at MIT
Cambridge, MA 02139
mstrunk@etexcorp.com

Employment

2005 - Present	Principal Scientist , ETEX Corporation, Cambridge, MA
2004	Research Scientist , Visen Medical, Woburn, MA
2001 - 2004	Research Fellow , USC Dept of Chemical Engineering, Columbia, SC
2000	Faculty , Albuquerque Technical Institute, Albuquerque, NM
1998 - 2001	Scientist , S.E.D. Medical Labs, Albuquerque, NM
1996 - 2001	Graduate Research Assistant , UNM Dept. of Chemistry, Albuquerque, NM
1996	Graduate Teaching Assistant , UNM Dept. of Chemistry, Albuquerque, NM
1990 - 1996	Senior Research Technologist , Chemical and Biochemical Toxicology, Lovelace Biomedical, Albuquerque, NM

Peer Reviewed Proceedings and Presentations

1. **M. Strunk**; S. Park; T. Ricketts; J. Chang; *Rates of Growth Factor Release from an Injectable Carrier of Autologous Blood and Bone Marrow*, Group de recherche interdisciplinaire sur les biomateriaux osteo-articulaires injectable (GRIBOI), April 2011, Boston, MA
2. Rosenberg, A.R., Camacho, N.R., **Strunk, M.**, Chang, J. *Injectable Calcium Phosphate Based Biomaterial Platform for the Delivery of Antibiotics in the Treatment of Infected Traumatic Fractures*, Group de recherche interdisciplinaire sur les biomateriaux osteo-articulaires injectable (GRIBOI), April 2011, Boston, MA
3. **M. Strunk**; S. Park; T. Ricketts; J. Chang; A. Tofighi; D. Kaplan, *Comparative Rates of Growth Factor Release from Carriers of Autologous Blood and Bone Marrow*, 56th Annual Meeting of the Orthopaedic Research Society, March 2010, New Orleans, LA
4. Wang, X., Ricketts, T., **Strunk, M.**, Tofighi, A., Kaplan, D., Chang, J., *Calcium Phosphate Cements as Growth factor and Cell Delivery Carriers for Bone Repair*,

- 9th New Jersey Symposium on Biomaterials Science and Regenerative Medicine, New Brunswick, NJ October 2008
5. A. Hina, C. Rey, M. Geiger, **M. Strunk**, *Modeling of Biomimetic apatite using a Surface Reactivity of Bone Mineral*, Society of Biomaterials 2008
6. Monika Geiger, Colleen Sherwin, Stephen Graunke, **Michael Strunk**, Ali Hina, Susan Sofia, *Real-time Monitoring of Conversion Reactions in Calcium Phosphate Matrix*, 8th World Biomaterials Congress, Amsterdam May 2008
7. A. Hina, **M. Strunk**, M. Geiger, *Factors Influencing Calcium Phosphate Cement Shelf Life*, 15th International Conference on Crystal Growth, Salt Lake City, UT, August 2007
8. **M.R. Strunk**, A. Hina, M. Geiger, *Modeling the Crystallization Kinetics of an Injectable Calcium Phosphate Cement from FTIR and XRD Data*, Society for Biomaterials Conference, Chicago, IL, April 2007
9. S. Woods, **M.R. Strunk**, *Physico-chemical and Histological Comparison of Injectable Calcium Phosphate Cements: α -BSM and CaPs*, Society for Biomaterials Conference, Chicago, IL, April 2007
10. **M.R. Strunk**, A.D. Rosenberg, M. Alolova, S. Woods, D.C. Moore, A.S. Turner, R.D. Welch, *Comparison of α -BSM[®] with a New, Enhanced Calcium Phosphate Cement (CaPs) in a Sheep Tibial Plateau Fracture Model*, Orthopaedic Trauma Association, 22nd Annual Meeting, Phoenix, AZ, October 2006
11. A. Hina, **M. Strunk**, M. Geiger, *Crystallization Kinetics of an Injectable Calcium Phosphate Based Cement*, Gordon Research Conference on Biomineralization, New London, New Hampshire, August 2006
12. **M. R. Strunk**, C. T. Williams. *Adsorption of aliphatic nitriles on oxide surfaces: A sum-frequency investigation*. Division of Colloid and Surface Chemistry, 226th ACS National Meeting, New York, NY, September, 2003
13. R. J. LeBlanc, I. Ortiz-Hernandez, **M. R. Strunk**, C. T. Williams. *In-situ vibrational spectroscopic investigation of solid-liquid catalytic interfaces*. Division of Colloid and Surface Chemistry, 225th ACS National Meeting, New Orleans, LA, March 2003
14. **Strunk, M.R.**, Williams, C.T. *In-situ characterization of acetonitrile-Pt/Al₂O₃ interfaces using IR-visible sum-frequency spectroscopy*, Southeastern Catalysis Society Symposium (SECS), Fall 2003
15. **Strunk, M.R.**, Williams, C.T. *Characterization of nitrile-metal oxide interfaces using IR-visible sum-frequency spectroscopy*, American Institute of Chemical Engineers (AIChE) National Meeting, Spring 2003
16. C. T. Williams, **M. R. Strunk**. *Characterization of nitrile/metal oxide interfaces using IR-visible sum-frequency generation*. Division of Colloid and Surface Chemistry, 224th ACS National Meeting, Boston, MA, August 2002
17. **M.R. Strunk**, C.T. Williams. *Characterization of nitrile/metal oxide interfaces using IR-visible sum-frequency generation*. Gordon Research Conference on Biomineralization, New London, New Hampshire, July 2002

18. **Strunk, M.R.**, Niemczyk, T.M. *Surface plasmon Fourier transform infrared spectroscopic investigation of a phase transition in crystalline self-assembled thiol terminated oligomers*, FACSS 2001
19. **Strunk, M.R.**, Niemczyk, T.M. *Surface plasmon induced vibrational Stark effect spectroscopy of interfaces*, PITTCO 2000
20. **Strunk, M.R.**, Niemczyk, T.M., Haaland, David, Clemen, Lucy *Interface sensitive multivariate modeling of reflection/absorption FTIR spectra*, FACSS 1997
21. Bechtold, W.E. **Strunk, M.R.** and M.J. Meyer: *S-Phenylcysteine in Albumin as a Biomarker*. Health Effects Institute Annual Meeting, Ashville, NC, April 1996
22. Henderson, R. F., W. E. Bechtold and **M. R. Strunk**: *Analysis of Benzene Metabolites and Glutathione in the Bone Marrow of B6C3F1 Mice*. Society of Toxicology Meeting, Baltimore, MD, March 1995.

Patents

1. Tofighi, A.N., Rosenberg, A.R., Chang, T.L., **Strunk, M.R.** Minimally invasive treatment of vertebra (MITV) using a calcium phosphate combination bone cement. *Provisional patent filed*
2. Rosenberg, A, **Strunk, M.R.**, Bondre, Shrikar and Gilles de Pelichy, Laurent. Porous Calcium Phosphate Bone Cement. *US/International patent filed*
3. **Strunk, M.R.**, Niemczyk, T.M., Brueck, S.J. Interface Sensitive Vibrational Stark Effect/FTIR Spectroscopy. *Provisional patent filed.*
4. **Strunk, M.R.** Bechtold, W.E. Automated Two-Dimensional Interface for Capillary Gas Chromatography S.N. 08/257,388 *United States patent issued.*

Peer Reviewed Publications

1. S. Park, A. Tofighi, X. Wang, **M. Strunk**, T Ricketts, J. Chang , D. L. Kaplan. Calcium Phosphate Combination Biomaterials as Human Mesenchymal Stem Cell (hMSC) Delivery Vehicles for Bone Repair. *Submitted to the Journal of Biomedical Research, January 2011*
2. Ortiz-Hernandez, I.; Owens, D. J.; **Strunk, M. R.**; Williams, C. T. Multivariate Analysis of ATR-IR Spectroscopic Data: Applications to the Solid-Liquid Catalytic Interface *Langmuir*; 2006; 22(6); 2629-2639
3. **Strunk, M.R.**, Williams, C.T. Aliphatic Nitrile Adsorption on Al₂O₃ and ZrO₂ as Studied by Total Internal Reflection Sum-Frequency Spectroscopy. *Langmuir*, 2003
4. L.L. Clemen, **M.R. Strunk**, T.M. Niemczyk, D.M. Haaland Attenuated Total Reflection of Dielectric/Metal Interfaces. *11th International Conference on Fourier Transform Spectroscopy, August, 1997*
5. Pyon, K.H., Kracko, D.A., **Strunk, M.R.**, Lewis, J.L. An Isotope Dilution Gas-Chromatography Mass Spectrometry Method for Trace Analysis of Xylene metabolites in Tissues. *Journal of Analytical Toxicology*, v.21 (#5) September 1997

Exhibit A

6. Bechtold, W.E. **Strunk, M.R.**, Thornton-Manning, J.R., and Henderson, R.F. Polyphenolic Metabolites in the Blood and Bone Marrow of Mice Exposed to Low-Levels of Benzene. *Abstracts of Papers of the American Chemical Society*, v. 212(pt. 1) August 1996
7. Bechtold, W.E. **Strunk, M.R.** S-Phenylcysteine in Albumin as a Benzene Biomarker *Environmental Health Perspectives*, v. 104(S6) Dec. 1996
8. Henderson, R. F., W. E. Bechtold, **M. R. Strunk**, J. R. Thornton-Manning, J. J. Waide: Analysis of Benzene Metabolites and Glutathione in the Bone Marrow of B6C3F1 Mice. *The Toxicologist* 15: 222, 1995
9. W. E. Bechtold, **M. R. Strunk**, J. R. Thornton-Manning, Henderson, R. F.: Benzene Metabolites Glutathione in the Blood and Bone Marrow of B6C3F1 Mice After Low Level Exposure. *ITRI Annual Report* 1994-95
10. Bechtold, W.E. **Strunk, M.R.**, Thornton-Manning, J.R., and Henderson, R.F. Analysis of Butadiene, Butadiene Monoxide, and Butadiene Dioxide by Gas Chromatography Gas Chromatography Mass Spectroscopy. *Chemical Research in Toxicology* v8(#2) pp. 182-7 March 1995
11. Bechtold, W.E., **Strunk, M.R.**, Chang, I.Y., Ward, J.B., Henderson, R.F. Species Differences in Urinary Metabolites: Comparisons of Ratios between Mice, Rats, and Humans. *Tox. and Applied Pharm.* 127:44-49, 1994
12. Bechtold, W.E., **Strunk, M.R.**, Chang I.Y., Henderson, R.F, Human Metabolism of 1,3 Butadiene. *ITRI Annual Report*. 92, 1991-92
13. Bechtold, W.E., **Strunk, M.R.** Multidimensional HPLC Analysis of Butadiene Monoepoxide/Guanosine Adducts with Electrochemical Detection. *ITRI Annual Report*. 92, 1991-92

Education

Project Management

Worcester Polytechnic Institute (Cambridge, MA)

Fundamentals

Research Fellow

Chemical Engineering

University of South Carolina (Columbia, SC)

Ph.D.

Chemistry

University of New Mexico (Albuquerque, NM)

SRC Research Fellow

Advanced Materials & Strategic Technologies

Motorola Semiconductor Products Sector (Mesa, AZ)

B.A.

Biochemistry

University of New Mexico (Albuquerque, NM)

Exhibit A

Awards

2005	ETEX Corporation, <i>"Accelerated Aging of Calcium Phosphate Bone Cements"</i>
2002	1 st Place, REU Mentored Project, "Biomimetic Interfaces" (Strunk, Hedjuk)
1998	Smith/Dow Award, Graduate Research in Chemistry

Exhibit B

Calorimetric measurement of heats of reactions during hardening.

